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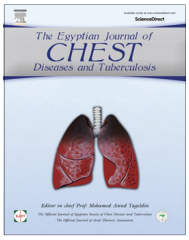

Serum resistin as an asthma marker and predictor of inhaled corticosteroid response in bronchial asthma in children

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KEYWORDS

Asthma;
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Abstract Adipokines are factors produced by adipose tissue, that may be proinflammatory (such as leptin and resistin) or anti-inflammatory (such as adiponectin). Effects of these adipokines on the lungs have the potential to evoke or exacerbate asthma.

Aim: Our aim was to assess if serum resistin level is changed in obese and non obese asthmatic children and if it can predict their responsiveness to inhaled glucocorticoids.

Methods: Serum levels of resistin, were measured in 60 asthmatic children (30 obese and 30 non obese asthmatic children), and in 30 age and sex matched healthy controls. The measurements were repeated in all asthmatics after 8 weeks of treatment with inhaled corticosteroids.

Results: Serum resistin levels were found to be significantly elevated in all asthmatic children than control group and it was significantly elevated in obese children, compared with asthmatic non obese and control children 35 ± 0.2 ng/mL vs 20 ± 0.25 vs 10 ± 0.11 ng/mL respectively ($F < 0.005$). There was negative correlation between asthma severity as detected by FEV1 and serum resistin levels. Serum resistin levels in all asthmatic children had no correlation with duration of asthma in years. Serum resistin level was significantly reduced in all asthmatic children after inhaled corticosteroids for 8 weeks. Also asthmatic children with good response to inhaled corticosteroids had high initial resistin levels compared to corticosteroids non-responder.

Conclusions: From these results we can conclude that resistin can be considered as a marker of asthma and its severity and high resistin levels can predict favourable anti-inflammatory effect of inhaled glucocorticoids suggesting that resistin may be a marker of steroid-sensitive genotype in asthma in children.

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Introduction

Asthma is a chronic inflammatory airway disease characterized by cough, chest tightness and wheezing, and it is associated with reversible or variable airway obstruction. However, the diagnosis and follow-up of the disease are currently based on symptoms and lung function measurements rather than on assessing the underlying inflammatory process [1]. Several asthma phenotypes with different inflammatory mechanisms have been described suggesting that asthma is not a single disease entity but a syndrome with different underlying causes and mechanisms [2]. Adipokines like leptin, adiponectin, resistin and adipsin are protein mediators secreted by adipocytes and macrophages within the adipose tissue [3]. Leptin and resistin are usually pro-inflammatory, while adiponectin has mainly anti-inflammatory properties [3]. There are some evidence suggesting connections between adipokines and asthma. However, further studies are needed to understand the role of adipokines in the pathogenesis of, and more importantly, in predicting treatment responses in different phenotypes of asthma. The efficacy of treatment with inhaled glucocorticoids seems to vary between asthmatic phenotypes, and phenotype-specific predictors of treatment response are needed [2]. The aim of the present study was to assess serum levels of resistin in obese and non obese asthmatic children and to assess if it can predict the responsiveness to inhaled corticosteroids in asthmatic children.

Subjects

Sixty asthmatic children (mean age 8 years, range 5–15 years) diagnosed according to GINA guide lines and followed up in asthma clinic in Pediatric department of Tanta University Hospital were enrolled in this study Asthmatic children were classified into 2 groups. Obese asthmatic children (group 1) and non obese asthmatics (group 2), in addition to 30 age and sex matched healthy children as control group (group 3).

Exclusion criteria

Children with chronic heart or pulmonary or endocrine disease and children who received inhaled glucocorticoids in the last 6 weeks before the study were excluded.

Methods

All children were subjected to full history taking, thorough clinical examination, BMI, pulmonary function test including FEV_1. Lung function, asthma symptom score, and serum levels of resistin were measured in all asthmatics and in controls. The asthmatics also filled in an asthma symptom questionnaire. The same measurements were repeated in all asthmatic children after 8 weeks of treatment with inhaled glucocorticoids 500 μg b.i.d. during weeks 1–4, and 250 μg b.i.d. during weeks 5–8). The study was approved by the ethics committee of Tanta University Hospital and parents of all subjects gave written informed consent.

Sample collection

Venous blood was collected for the assessment of serum levels of resistin determined by enzyme-immuno-assay (EIA) by using commercial reagents (DuoSet ELISA, R&D Systems Europe Ltd, Abindgon, U.K. Netherlands) [4].

Asthma symptoms questionnaire

Asthma symptoms were recorded by using written symptom questionnaire. Cough, chest tightness, wheezing and nocturnal asthma symptoms were each scored from 0 to 3 yielding a total score from 0 to 12 points [5].

Statistics

Differences in resistin levels between asthmatics and controls were analysed with *t*-test, where appropriate. Pearson correlation coefficient was used to analyse correlations between resistin levels and lung function indices. Changes in serum levels of resistin before and after inhaled glucocorticoids treatment were analysed with a paired *t*-test. Results were presented as mean ± SD, and *P*-value < 0.05 was considered as significant. SPSS 15.0.1 software

Results

The data base of all groups is given in Table 1. There were no statistical significant differences as regards age, sex percentages between all asthmatics and controls. BMI was statistically sig-

Table 1 The demographic s of the studied groups.

	Obese asthmatics	Non-obese asthmatics	Controls	*F* Value
Age (Years) Mean ± SD	8.25 ± 1.5	8.20 ± 1.5	8.3 ± 1.25	$F > 0.5$
Sex				
M	12	12	12	$F > 0.5$
F	18	18	18	
Duration of asthma (years) mean ± SD	5.5 ± 2.5	5.00 ± 2.00	–	$F > 0.5$
BMI Mean ± SD	34.2 ± 2.1	22 ± 1.1	22 ± 1.4	$F < 0.05$
Eosinophils (Cell/ml) Mean ± SD	400 ± 20	380 ± 40	80 ± 10	$F < 0.05$
IgE Mean ± SD	280 ± 10	270 ± 15	50 ± 15	$F < 0.05$

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Table 2 Serum resistin levels in obese asthmatic and non-obese asthmatic children and controls.

	Obese asthmatics	Non-obese asthmatics	Controls	*F* value
Serum Resistin (ng/ml) mean ± SD	35 ± 0.2 *P* < 0.05	20 ± 0.25	10 ± 0.11	*F* < 0.05

nificantly higher in obese asthmatics than non obese asthmatics and controls (34.2 ± 2.1 vs 22 ± 1.1 vs 22 ± 1.4 $F < 0.05$) respectively. All asthmatic children obese and non-obese had significantly higher serum levels IgE and higher blood eosinophil count than controls (280 ± 10 vs 270 ± 15 vs 50 ± 15 respectively $\boldsymbol{F} < 0.05$ and 400 vs 380 ± 40 vs ± 10 respectively $F < 0.05$), but there was no statistical differences between obese asthmatics and non-obese asthmatics as regards serum IgE levels or peripheral blood eosinophils. Obese asthmatics had significantly higher serum levels of resistin than non obese asthmatics than controls (35 ± 0.2 vs 20 ± 0.25 vs 10 ± 0.11 respectively $F < 0.05$) as in Table 2. Serum resistin showed a negative correlation with asthma severity as evidenced by FEV1 as seen in Fig. 1. No correlation was found between serum levels of resistin and duration of asthma among all asthmatic children as in Table 3.

Serum levels of resistin were significantly reduced in all asthmatic children after corticosteroid therapy for 8 weeks as in Table 4. Twenty asthmatic children had relatively higher initial levels of serum resistin and 40 asthmatic children had relatively less higher initial level of serum resistin (42 ± 2.1 vs 28 ± 2.6 respectively $P < 0.05$) as in Table 5. Asthmatic children either obese or non-obese with initial higher levels of resistin showed significant response to inhaled corticosteroids for eight weeks than asthmatics with relatively low high resistin levels as evidenced by marked reduction of their asthma questioner score after inhaled corticosteroids for 8 weeks than in children with relatively less higher initial levels of serum resistin as in Table 6.

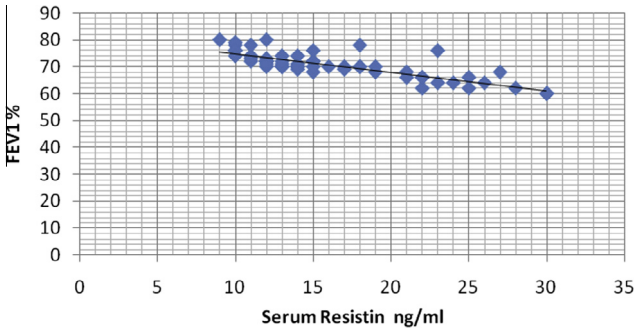

Figure 1 The correlation between serum resistin levels and FEV1.

Table 3 Correlation between duration of asthma in asthmatic children (in years) and mean serum resistin levels.

	Duration of asthma in all asthmatics (years)	Mean serum resistin in all asthmatics (obese and non obese)	*P* value
Mean SD Correlation coefficient (r)	35 ± 0.2 2.55	27.7 ± 0.25	*P* > 0.05

Discussion

Asthma is often considered as a single disease entity, but it is actually a syndrome with many different pathological pathways ultimately leading to quite similar clinical presentation of variable airway obstruction with chest tightness, wheezing and cough [1]. The role of adipokines varies between these different inflammatory processes. Resistin is associated with different inflammatory states [3] but there are only a few previous publications on resistin in children with asthma [5]. Nuclear factor κB (NF-κB) is a transcription factor inducing the expression of many pro-inflammatory adipokines [6]. Inhaled glucocorticoids is a corner stone in treatment of asthma. Inhaled glucocorticoids exert their anti-inflammatory effects through a wide variety of mechanisms, of which inhibition of NF-κB is one of the most important mechanism [7]. In the present study, we investigated the serum resistin in obese and non-obese asthmatic children. Our results showed that mean resistin level was significantly higher in all asthmatic children (obese and non-obese) compared with control group. and resistin levels were significantly higher in obese asthmatic children than non obese asthmatics. Also there was a negative correlation between mean resistin levels and asthma severity. This relation may be explained by the finding that resistin is an endogenous agonist of Toll-like receptor 4 (TLR4) which leads to activation of various genes involved in asthmatic inflamma-

Table 4 The serum levels of resistin before and after corticosteroid therapy.

	Obese asthmatics	Non-obese asthmatics	*P* value of paired *T* test
Initial serum resistin before treatment	35 ± 0.2	20 ± 0.25	*P* < 0.05
Serum resistin after corticosteroid therapy	15. ± 1.1	12. ± 1.2	*P* < 0.05

Table 5 Patients with initial higher levels of resistin.

	Asthmatic children with relatively more higher initial levels of resistin	Asthmatic children with relatively less l higher initial levels of resistin	*P* value
Number of patients	20	40	
Serum resistin (ng/ml)	42 ± 2.1	28 ± 2.6	*P* < 0.05

Table 6 Mean asthma questioner score in asthmatic children with initial higher levels of serum resistin and asthmatic children with les higher serum resistin levels before and after inhaled corticosteroids.

	Asthmatic children with initial more higher resistin levels (no = 20)	Asthmatic children with initial less higher resistin levels (no = 40)
Serum resistin	42 ± 2.1	28 2 ± .6
Mean asthma questioner score before treatment	12	12
Mean asthma questioner score treatment after	1	5

tion through NF-kB pathway [8]. Our results are coincident with the finding of LaRochelle et al. who showed that patients with moderate to severe asthma had higher levels of resistin than controls, and resistin levels were increased with increasing disease severity [9]. On the contrary, Kim and colleagues found that resistin levels were lower in atopic asthmatics than in healthy controls, and resistin was associated with lower markers of atopy or bronchial responsiveness [10]. However, Arshi et al. did not find any differences in resistin levels between patients with asthma and healthy controls [5]. Conflicting results are likely to be explained by differences in patient selection.

Our results showed also high pre-treatment resistin levels were associated with a more pronounced improvement of symptoms in asthmatic children after inhaled corticosteroids treatment indicating a better steroid-response. This can be explained by the fact that resistin may be able to enhance the production of proinflammatory cytokines IL-6 and TNF-α in human macrophages and this effect may be inhibited with inhaled corticosteroids. Also, the expression of resistin itself has been reported to be enhanced by inflammatory factors like IL-1, IL-6, TNF-α and LPS by an NF-κB dependent manner [11,12]. Therefore high resistin levels may reflect an asthmatic phenotype characterized by increased NF-κB activity and hence favourable response to glucocorticoids, the anti-inflammatory action of which is primarily based on their suppressive effect on NF-κB [12].

Conclusion

High resistin levels were present in obese and non obese asthmatic children and were correlated with asthma severity suggesting that the link between adipokine resistin and asthma is not restricted to obesity, and resistin can be considered as a marker of asthma and asthma severity. Also higher resistin levels predicted favourable anti-inflammatory effect of inhaled glucocorticoids suggesting that resistin may be a feature and biomarker of steroid-sensitive phenotype of asthma.

Compliance with ethical statement

1. All authors don't suffer from any conflicts to disclose.
2. The study included human participants.
3. Ethical approval the study was approved by the ethical committee of Tanta faculty of medicine
4. Informed consent Informed consent was obtained from all individual participants included in the study or by their parents.

Fund

No fund.

Conflicts of interest

No conflicts of interest for both authors.

References

[1] E.D. Bateman, S.S. Hurd, P.J. Barnes, J. Bousquet, J.M. Drazen, M. FitzGerald, P. Gibson, K. Ohta, P. O'Byrne, S.E. Pedersen, E. Pizzichini, S.D. Sullivan, S.E. Wenzel, H.J. Zar, Global strategy for asthma management and prevention: GINA executive summary, Eur. Respir. J. 31 (2008) 143–178.
[2] G.P. Anderson, Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease, Lancet 372 (2008) 1107–1119.
[3] G. Fantuzzi, Adipose tissue, adipokines, and inflammation, J. Allergy Clin. Immunol. 115 (2005) 911–919.
[4] N. Guler, E. Kirerleri, U. Ones, Z. Tamay, N. Salmayenli, F. Darendeliler, Leptin: does it have any role in childhood asthma?, J Allergy Clin. Immunol. 114 (2004) 254–259.
[5] M. Arshi, J. Cardinal, R.J. Hill, P.S. Davies, C. Wainwright, Asthma and insulin resistance in children, Respirology 15 (2010) 779–784.
[6] N. Silswal, A.K. Singh, B. Aruna, S. Mukhopadhyay, S. Ghosh, N.Z. Ehtesham, Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway, Biochem. Biophys. Res. Commun. 334 (2005) 1092–1101.
[7] P.J. Barnes, Molecular mechanisms and cellular effects of glucocorticosteroids, Immunol. Allergy Clin. North Am. 25 (2005) 451–468.
[8] A. Tarkowski, J. Bjersing, A. Shestakov, M.I. Bokarewa, Resistin competes with lipopolysaccharide for binding to toll-like receptor 4, J. Cell Mol. Med. 14 (2008) 1419–1431.
[9] J. Larochelle, J. Freiler, J. Dice, L. Hagan, Plasma resistin levels in asthmatics as a marker of disease state, J. Asthma 44 (2007) 509–513.
[10] K.W. Kim, Y.H. Shin, K.E. Lee, E.S. Kim, M.H. Sohn, K.E. Kim, Relationship between adipokines and manifestations of childhood asthma, Pediatr. Allergy Immunol. 19 (2008) 535–540.
[11] Global Initiative for Asthma (GINA), Global Strategy for Asthma Management and Prevention Available from: http://WWW.ginasthma.org2008.
[12] Leivo-Korpelal, L. Lehtimäki, K. Vuolteenaho, R. Nieminen, K. Hannu, S. Saarelainen, E. Moilanen, Adipokine resistin predicts antiinflammatory effect of glucocorticoids in asthma, J. Inflamm. 9 (2011) 35–40.

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